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12 Mars 1997(12.03.97)	
International publication No. WO97/06157	

Pursuant to the addressee's request of 07 March 1997 .

1. [X] the International Bureau hereby transmits a copy of the following application(s), the priority of which was claimed in the international application: PCT/AU96/00495

country	date	number
GB	08 August 1995(08.08.95)	9516276.4

An invoice for furnishing the above-mentionned copy(ies) will be sent under separate cover.

2. [ ] the International Bureau informs the addressee that the priority document(s) identified below has (have) not been received; consequently the requested copy(ies) cannot be furnished.

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Form PCT/IB/353 (July 1992)

PCT/AU96/00495

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PRIORITY DOCUMENT

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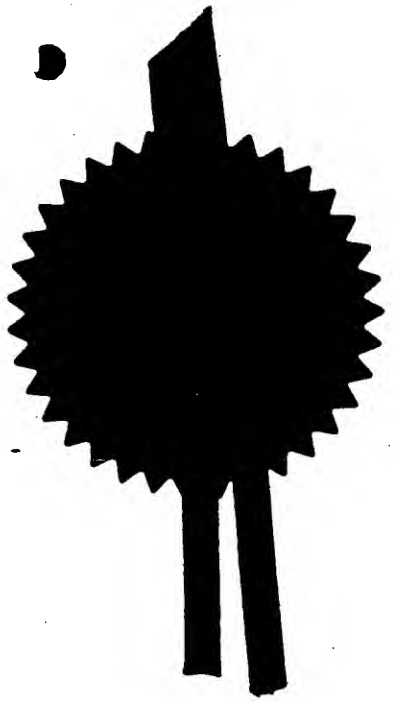

Signed

Dated 16.7.96

official use

08 AUG 1995

Your reference
HQ/GR2122

9516276.4

Notes
Please type, or write in dark ink using CAPITAL letters. A prescribed fee is payable for a request for grant of a patent. For details, please contact the Patent Office (telephone 071-438 4700).

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The Patent Office

Request for grant of a Patent

Form 1/77

Patents Act 1977

1 Title of invention

1 Please give the title of the invention

CHEMICAL COMPOUNDS

2 Applicant's details

☐ First or only applicant

2a If you are applying as a corporate body please give:

Corporate name
BIOTA SCIENTIFIC MANAGEMENT LTD

Country *(and State of incorporation, if appropriate)*
AUSTRALIA

2b If you are applying as an individual or one of a partnership please give in full:

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Forenames

2c **In all cases,** please give the following details:

Address

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GLEN IRIS
VICTORIA 3146

UK postcode
(if applicable)

Country AUSTRALIA

ADP number
(if known) 6782601001 pg

2d, 2e and 2f:
If there are further applicants please provide details on a separate sheet of paper.

S cond applicant (if any)

2d If you are applying as a corporate body please give:

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Country *(and State of incorporation, if appropriate)*

2e If you are applying as an individual or one of a partnership please give in full:

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Forenames

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3
An address for service in the United Kingdom must be supplied.
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3 Address for service details

3a Have you appointed an agent to deal with your application?

Yes [X] No [ ] ➡ *go to 3b*

⬇ *Please give details below*

Agent's name
HELEN KAYE QUILLIN
Agent's address
GLAXO HOUSE
BERKELEY AVENUE
GREENFORD
MIDDLESEX
Postcode UB6 0NN

Agent's ADP number 0647057902

3b:
If you have appointed an agent, all correspondence concerning your application will be sent to the agent's United Kingdom address.

3b If you have not appointed an agent please give a name and address in the United Kingdom to which all correspondence will be sent:

Name

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ADP number
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Daytime telephone number *(if available)*

Additional Agents
(See Page 2 No. 3a)

NAME(S)	Alan HESKETH Laurence David JENKINS Michael DADSON Peter I. DOLTON Hugh B. DAWSON Wendy Anne. FILLER Alison GALLAFENT Michael GARRETT Catriona McLeod HAMMER Watson Palmer McMUNN Michael John STOTT
ADDRESS	Glaxo Wellcome plc Glaxo House Berkeley Avenue Greenford Middlesex UB6 ONN Great Britain

4 Reference number

4 Agent's or applicant's reference number *(if applicable)* HQ/GR2122

5 Claiming an earlier application date

5 Are you claiming that this application be treated as having been filed on the date of filing of an earlier application?

Please mark correct box

Yes ☐ No ☒ ➡ *go to 6*

⬇

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☐ number of earlier application or patent number

☐ filing date *(day month year)*

☐ and the Section of the Patents Act 1977 under which you are claiming:

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15(4) (Divisional) ☐ 8(3) ☐ 12(6) ☐ 37(4) ☐

6 Declaration of priority

6 *If you are declaring priority from a PCT Application please enter 'PCT' as the country and enter the country code (for example, GB) as part of the application number.*

Please give the date in all number format, for example, 31/05/90 for 31 May 1990.

6 If you are declaring priority from previous application(s), please give:

Country of filing	Priority application number *(if known)*	Filing date *(day,month,year)*

7

The answer must be 'No' if:
- any applicant is not an inventor
- there is an inventor who is not an applicant, or
- an applicant is a corporate body

8

Please supply duplicates of claim(s), abstract, description and drawing(s).

Please mark correct box(es)

9

You or your appointed agent (see Rule 90 of the Patents Rules 1990) must sign this request.

Please sign here ➡

A completed fee sheet should preferably accompany the fee.

7 Inventorship

7 Are you (the applicant or applicants) the sole inventor or the joint inventors?

Please mark the correct box

Yes ☐ No ☒ ➡

A statement of Inventorship on Patents Form 7/77 will need to be filed (see Rule 15).

8 Checklist

8a Please fill in the number of sheets for each of the following types of document contained in this application.

Continuation sheets for this Patents Form 1/77	1		
Claim(s)		Description	27
Abstract		Drawing(s)	

8b Which of the following documents also accompanies the application?

Priority documents *(please state how many)*	
Translation(s) of Priority documents *(please state how many)*	
Patents Form 7/77 - Statement of Inventorship and Right to Grant *(please state how many)*	
Patents Form 9/77 - Preliminary Examination/Search	
Patents Form 10/77 - Request for Substantive Examination	

9 Request

I/We request the grant of a patent on the basis of this application.

Signed Helen K Quillin Date 07/08/1995

H K Quillin Agent for the Applicants *(day month year)*

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CHEMICAL COMPOUNDS

This invention relates to a new class of chemical compounds and to their use in medicine. In particular the invention concerns novel dihydropyran derivatives, methods for their preparation, pharmaceutical formulations thereof and their use as antiviral agents.

Enzymes with the ability to cleave N-acetyl neuraminic acid (NANA), also known as sialic acid, from other sugars are present in many microorganisms. These include bacteria such as Vibrio cholerae, Clostridium perfringens, Streptococcus pneumoniae, and Arthrobacter sialophilus, and viruses such as influenza virus, parainfluenza virus, mumps virus, Newcastle disease virus, and Sendai virus. Most of these viruses are of the orthomyxovirus or paramyxovirus groups, and carry a neuraminidase activity on the surface of the virus particles.

Many of the neuraminidase-possessing organisms are major pathogens of man and/or animals, and some, such as influenza virus and Newcastle disease virus, cause diseases of enormous economic importance.

It has long been thought that inhibitors of neuraminidase activity might prevent infection by neuraminidase-bearing viruses. Most of the known neuraminidase inhibitors are analogues of neuraminic acid, such as 2-deoxy-2,3-didehydro-N-acetylneuraminic acid (DANA) and its derivatives. See, e.g., Meindl et al., Virology 1974 58 457-63. International Application Publication No. WO91/16320 describes a number of analogues of DANA active both in vitro and in vivo against viral neuraminidase and useful in the treatment of influenza.

We have now found a novel class of dihydropyran derivatives which are active against the influenza virus.

The invention therefore provides, in a first aspect, compounds of formula (I)

Suitable hydrocarbon groups represented by R^6 and/or R^5 include C_{1-20}alkyl, such as propyl, butyl, pentyl, hexyl, heptyl, octanyl, nonyl, decyl, undecyl and dodecyl, C_{5-7}cycloalkyl groups, such as cyclohexyl, phenyl and aralkyl groups such as benzyl. Suitable substituents for the hydrocarbon groups represented by R^6 and/or R^5 include Br, Cl, F, I, CF_3, NH_2, substituted amino groups such as $NHCO(C_4H_{10})$, alkoxy groups such as methoxy, and hydroxy.

When R^5 and/or R^6 represents a heteroaromatic group, this will suitably be a pyridyl group optionally substituted by one or more of C_{1-6}alkyl, Br, Cl, F, I and CF_3.

Preferably R^5 represents H, C_{1-6}alkyl or benzyl.

Preferably R^6 represents optionally substituted C_{1-20}alkyl or benzyl.

More preferably R^5 represents H, C_{1-3}alkyl or benzyl and R^6 represents C_{1-12}alkyl optionally substituted by an unsubstituted or substituted amine, or benzyl.

Preferably R^2 represents COR^9.

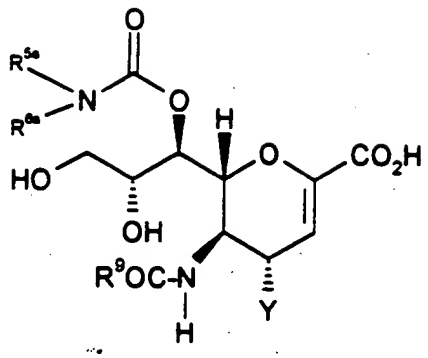
Where R^3 represents $C(=NR^{11})NR^{12}R^{13}$, suitably two of R^{11}, R^{12} and R^{13} represent H and the other of R^{11}, R^{12} and R^{13} is selected from H, C_{1-6}alkyl, such as methyl, NH_2, OH, CN or NO_2.

Preferably NR^3R^4 represents amino or guanidino, more preferably guanidino.

Preferably R^9 represents methyl or trifluoromethyl, more preferably methyl.

Preferably X represents O.

By "a pharmaceutically acceptable derivative" is meant any pharmaceutically acceptable salt, ester, or salt of such ester, of a compound of formula (I) or any other compound which, upon administration to the recipient, is capable of



(Ia)

wherein:
R^9 is as defined for formula (I);
R^{5a} represents H, C_{1-12}alkyl or benzyl;
R^{6a} represents optionally substituted C_{1-12}alkyl or benzyl;
Y represents an amino or guanidino group;
and pharmaceutically acceptable salts or esters thereof.

When R^{6a} represents optionally substituted C_{1-12}alkyl, suitable substituents include substituted and unsubstituted amines.

Particular compounds according to the invention include:

(4S,5R,6R)-5-Acetylamino-6-(1R-heptylcarbamoyloxy-2R,3-dihydroxy-propyl)-4-guanidino-5,6-dihydro-4H-pyran-2-carboxylic acid;
(4S,5R,6R)-5-Acetylamino-6-(1R-dodecylcarbamoyloxy-2R,3-dihydroxy-propyl)-4-guanidino-5,6-dihydro-4H-pyran-2-carboxylic acid;
(4S,5R,6R)-5-Acetylamino-6-{1R-[(6-amino-hexyl)carbamoyloxy]-2R,3-dihydroxypropyl}-4-guanidino-5,6-dihydro-4H-pyran-2-carboxylic acid;

and pharmaceutically acceptable derivatives thereof.

References hereinafter to a compound of the invention include the compounds of formula (I) and pharmaceutically acceptable derivatives thereof.

The compounds of formula (I) possess antiviral activity. In particular these compounds ar inhibitors of viral neuraminidase of orthomyxovirus s and paramyxoviruses in particular neuraminidas , for example the viral

the discretion of the attendant physician or veterinarian. In general however a suitable dose will be in the range of from about 0.1 to 750mg/kg of bodyweight per day, preferably in the range of 0.5 to 60 mg/kg/day, most preferably in the range of 1 to 20mg/kg/day.

Treatment is preferably commenced before or at the time of infection and continued until virus is no longer present in the respiratory tract. However the compounds are also effective when given post-infection, for example after the appearance of established symptoms.

Suitably treatment is given 1-4 times daily and continued for 3-7, e.g. 5 days post infection depending upon the particular compound used.

The desired dose may be presented in a single dose or as divided doses administered at appropriate intervals, for example as two, three, four or more sub-doses per day.

The compound is conveniently administered in unit dosage form for example containing 10 to 1500mg, conveniently 20 to 1000mg, most conveniently 50 to 700mg of active ingredient per unit dosage form.

While it is possible that, for use in therapy, a compound of the invention may be administered as the raw chemical it is preferable to present the active ingredient as a pharmaceutical formulation

The invention thus further provides a pharmaceutical formulation comprising a compound of formula (1) or a pharmaceutically acceptable salt or derivative thereof together with one or more pharmaceutically acceptable carriers therefor and, optionally, other therapeutic and/or prophylactic ingredients. The carrier(s) must be 'acceptable' in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

Pharmaceutical formulations include those suitable for oral, rectal, nasal, topical (including buccal and sub-lingual), vaginal or par nteral (including intramuscular, sub-cutaneous and intrav nous) administration or in a form

an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilising agents, dispersing agents, suspending agents, thickening agents, or colouring agents.

Formulations suitable for topical administration in the mouth include lozenges comprising active ingredient in a flavoured base, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert base such as gelatin and glycerin or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Pharmaceutical formulations suitable for rectal administration wherein the carrier is a solid are most preferably presented as unit dose suppositories. Suitable carriers include cocoa butter and other materials commonly used in the art, and the suppositories may be conveniently formed by admixture of the active compound with the softened or melted carrier(s) followed by chilling and shaping in moulds.

Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or sprays containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

For administration to the respiratory tract (including intranasal administration) according to the method of the invention the neuraminidase inhibitors may be administered by any of the methods and formulations employed in the art for administration to the respiratory tract.

Thus in general the compounds may be administered in the form of a solution or a suspension or as a dry powder.

Solutions and suspensions will generally be aqueous for example prepared from water alone (for example sterile or pyrogen-free water) or water and a physiologically acceptable co-solvent (for example ethanol, propylene glycol, poly thlene glycols such as PEG 400).

for example of the order of 5 microns or less. Such a particle size may be obtained by means known in the art, for example by micronisation.

When desired, formulations adapted to give sustained release of the active ingredient may be employed.

The compounds of the invention may also be used in combination with other therapeutic agents, for example other anti-infective agents. In particular the compounds of the invention may be employed with other antiviral agents. The invention thus provides in a further aspect a combination comprising a compound of formula (I) or a pharmaceutically acceptable salt or derivative thereof together with another therapeutically active agent, in particular an antiviral agent.

The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus such formulations comprising a combination as defined above together with a pharmaceutically acceptable carrier therefor comprise a further aspect of the invention.

Suitable therapeutic agents for use in such combinations include other anti-infective agents, in particular anti-bacterial and anti-viral agents such as those used to treat respiratory infections. For example, other compounds effective against influenza viruses, such as amantadine, rimantadine and ribavirin, may be included in such combinations.

The individual components of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations.

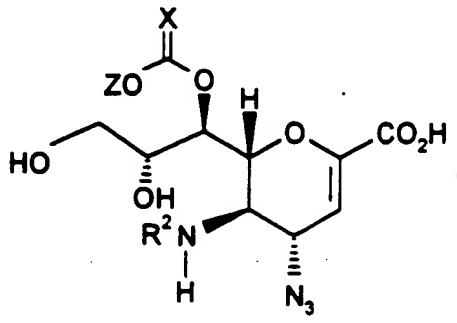
When the compounds of the invention are used with a second therapeutic agent active against the same virus the dose of each compound may either be the same as or differ from that employed when each compound is used alone. Appropriate doses will be readily appreciated by those skilled in the art.

or protected derivatives thereof wherein Z represents an activating group, for example para-nitrophenyl, by reaction with a compound of formula HNR^5R^6 in the presence of a base, such as an organic base, for example, pyridine and, preferably, a suitable catalyst, such as dimethylaminopyridine (DMAP).

Compounds of formula (I) may also be prepared from other compounds of formula (I) by interconversion reactions. For example, compounds wherein R^3 and R^4 are other than H may be prepared by derivatisation of the corresponding compound wherein R^3 and/or R^4 are H. In particular, compounds of formula (I) wherein R^3 represents $C(=NR^{11})NR^{12}R^{13}$ may be prepared from corresponding compounds of formula (III) wherein R^3 is H, for example, by reaction with pyrazolcarboxamidine, or a derivative thereof.

Similarly, compounds of formula (I) may be converted to their pharmaceutically acceptable derivatives, e.g. salts or esters, by conventional techniques.

Compounds of formula (II) may be prepared from the corresponding compounds of formula (IV):



(IV)

or protected derivatives thereof, wherein Z is as previously defined, analogously to the preparation of compounds of formula (I) from compounds of formula (III). Intermediates of formula (III) and (IV) may be prepared from the corresponding compounds of formula (V):

Hydroxy or carboxy groups may be protected, for example, by aralkyl groups, such as benzyl, diphenylmethyl or triphenylmethyl groups, acyl groups, such as acetyl, acetal, silicon protecting groups, such as trimethylsilyl groups, or as tetrahydropyran derivatives.

Removal of any protecting groups present may be achieved by conventional procedures.

Where it is desired to isolate a compound of the invention as a salt, for example as an acid addition salt, this may be achieved by treating the free base of general formula (I) with an appropriate acid, preferably with an equivalent amount, or with creatinine sulphate in a suitable solvent (e.g. aqueous ethanol).

The present invention is further described by the following examples which are for illustrative purposes only and should not be construed as a limitation of the invention.

Example 1
(4S,5R,6R)-5-Acetylamino-4-amino-6-(1R-heptylcarbamoyloxy-2R,3-dihydroxy-propyl)-5,6-dihydro-4H-pyran-2-carboxylic acid trifluoroacetate

Intermediate (1): (4S,5R,6R)-5-Acetylamino-4-azido-6-[(S)-hydroxy-(2-oxo-[1,3]dioxolan-4R-yl)-methyl]-5,6-dihydro-4H-pyran-2-carboxylic acid methyl ester

To a suspension of (4S,5R,6R)-5-Acetylamino-4-azido-6-(1R,2R,3-trihydroxy-propyl)-5,6-dihydro-4H-pyran-2-carboxylic acid methyl ester (8.2g) in dry acetonitrile (100ml) and dry dichloromethane (200ml) was added 4-dimethylaminopyridine (8.6g). A 20% solution of phosgene in toluene (18ml) was added slowly dropwise and the reaction mixture was stirred at room temperature for 2 hours. The solution was then added to ice cold 1M potassium dihydrogen orthophosphate solution (400ml) and extracted with ethyl acetate (350mlx3). The combined organic extracts were washed with saturated aqueous NaCl (30ml), dried (Na_2SO_4), and the solvent removed under vacuum to yield an orang foam which was purified by flash chromatography on a silica

Analysis Found : C, 45.8; H, 6.5; N, 7.75.
$C_{19}H_{33}N_3O_8.CF_3CO_2H$ requires C, 46.2; H, 6.3; N, 7.7

Example 2
(4S,5R,6R)-5-Acetylamino-6-(1R-heptylcarbamoyloxy-2R,3-dihydroxypropyl)-4-guanidino-5,6-dihydro-4H-pyran-2-carboxylic acid trifluoroacetate

Intermediate (3): (4S,5R,6R)-5-Acetylamino-6-(1R-heptylcarbamoyloxy-2R,3-dihydroxypropyl)-4-[2,3-bis(tert-butoxycarbonyl)-guanidino]-5,6-dihydro-4H-pyran-2-carboxylic acid methyl ester

A solution of the compound of Example 1 (190mg), triethylamine (0.1ml) and N,N'-bis-t-butoxycarbonyl-1H-pyrazole-1-carboxamidine (179mg) in dry methanol (3ml) was stirred under nitrogen for 48 hours and then evaporated under vacuum. The residue obtained was purified by flash chromatography on a silica column (Merck 9385, ethyl acetate/glacial acetic acid 95:5) to give the title compound (218mg) as a white solid.
NMR(d_6-DMSO) δ 8.17 (1H, d), 7.90 (1H, d), 7.13 (1H, t), 5.67 (1H, s), 4.80 (1H, d), 4.68 (1H, t), 4.39 (1H, d), 3.99 (1H, m), 3.83 (1H, m), 3.40 (1H), 3.24 (1H), 2.88 (2H, m), 1.92 (3H, s), 1.44 (9H, s), 1.40 (9H, s), 1.23 (10H, m), 0.86 (3H, t).
m/z MH^+=674.4

(4S,5R,6R)-5-Acetylamino-6-(1R-heptylcarbamoyloxy-2R,3-dihydroxypropyl)-4-guanidino-5,6-dihydro-4H-pyran-2-carboxylic acid trifluoroacetate

A solution of Intermediate 3 (104mg) in dry dichloromethane (1ml) and trifluoroacetic acid (1ml) was stirred under nitrogen for 2 hours and then evaporated under vacuum. The residue was taken up in methanol (2 drops) and precipitated using diethyl ether (5ml) to yield a white solid which was purified by preparative Hplc (Microsorb C18) using a water/acetonitrile/trifluoroacetic acid elution gradient. The freeze-dried solid obtained was taken up in methanol (2 drops) and precipitated using diethyl ether (5ml) to give the title compound (29mg) as a white powder.
NMR(d_6-DMSO) δ 7.98 (1H, br d), 7.57 (1H, br d), 7.40 (3H, br s), 7.17 (1H, br t), 5.54 (1H, br d), 4.82 (1H, d), 4.2-4.38 (2H, 2xdd), 3.96 (1H, q), 3.82 (1H, td), ~3.3 (2H, m), 2.88 (2H, q), 1.77 (3H, s), 1.12-1.49 (10H, m), 0.87 (3H, t).
m/z MH^+=474. MS calcd. for $C_{20}H_{36}N_5O_8$ (MH^+): 474.2564. Found 474.2562

Intermediate (6): (4S,5R,6R)-5-Acetylamino-4-amino-6-[(S)-dodecylcarbamoyloxy-(2-oxo-[1,3]dioxolan-4R-yl)-methyl]-5,6-dihydro-4H-pyran-2-carboxylic acid benzhydryl ester

A mixture of Intermediate 5 (1.139g) and triphenylphosphine (517mg) in dry tetrahydrofuran (20ml) was heated at 40^0 under nitrogen for 24 hours. To this was added triethylamine (11ml) and water (17ml) and the reaction mixture was heated at 40^0 for 2 hours and then evaporated to yield a yellow solid which was purified by flash chromatography on a silica column (Merck 9385, chloroform/methanol 15:1) to give the title compound (761mg) as a yellow foam.
TLC silica (chloroform/methanol 15:1) R_f 0.14
m/z MS calcd. for $C_{39}H_{56}N_3O_8$ (MH^+):694.4067. Found 694.4062

Intermediate (7): (4S,5R,6R)-5-Acetylamino -6-[(S)-dodecylcarbamoyloxy-(2-oxo-[1,3]-dioxolan-4R-yl)-methyl]-4-[2,3-bis(tert-butoxycarbonyl)-guanidino-5,6-dihydro-4H-pyran-2-carboxylic acid benzhydryl ester

A suspension of Intermediate 6 (670mg) and bis (t-butoxycarbonyl)-1H-pyrazole-1-carboxamidine (390mg) in dry tetrahydrofuran (8ml) was stirred under nitrogen at 35^0 for 48 hours and then evaporated under vacuum to yield an off-white foam which was purified by flash chromatography on a silica column (Merck 9385, ethyl acetate/petroleum ether (40-60) 1:2) to give the title compound (815mg) as a white solid.
TLC silica (ethyl acetate/petroleum ether (40-60) 1:2) R_f 0.13
m/z MH^+=936.6

(4S,5R,6R)-5-Acetylamino -6-(1R-dodecylcarbamoyloxy-2R,3-dihydroxypropyl)-4-guanidino -5,6-dihydro-4H-pyran-2-carboxylic acid trifluoroacetate

A solution of Intermediate 7 (637mg) in glacial acetic acid/water 4:1 (20ml) was heated at 85^0 for 2 hours and then evaporated under vacuum to yield a white solid which was stirred in dry dichloromethane (6ml) and trifluoroacetic acid (5ml) for 26 hours. The solvent was removed under vacuum to yield a green foam which was purified by reverse phase silica column chromatography (Merck, LiChroprep RP-18, water/acetonitrile/trifluoroacetic acid 50:50:1) to give the title compound (209mg) as a freeze-dried white powd r.

Intermediate (9): (4S,5R,6R)-5-Acetylamino-4-azido-6-{(S)-[(2-oxo-[1,3]dioxolan-4R-yl)-(6-tert-butoxycarbonylaminohexyl)-carbamoyloxy]-methyl}-5,6-dihydro-4H-pyran-2-carboxylic acid methyl ester

To a solution of Intermediate 8 (1.15 g) in dry pyridine was added 4-dimethylaminopyridine (648 mg) and N-Boc-1,6-diaminohexane hydrochloride (670 mg). The solution was stirred at room temperature for 18 hours. 2M aqueous hydrochloric acid (150 ml) was added to the solution and extracted with ethyl acetate (50 ml x 2). The combined organic extracts were washed with saturated aqueous NaCl (10 ml), dried (Na_2SO_4) and the solvent removed under vacuum to yield a yellow foam which was purified by flash chromatography on a silica column (Merck 9385, ethyl acetate/ cyclohexane 4:1) to give the title compound (1.155 g) as a pale yellow foam.

NMR ($CDCl_3$) δ 6.31 (1H, br.d), 5.95 (3H, d), 5.42 (1H, dd), 4.5-5.2 (7H, m), 3.80 (3H, s), 3.0-3.4 (5H, m), 2.06 (3H, s), 1.50 (4H, m), 1.44 (9H, s), 1.34 (4H, m).

TLC silica (ethyl acetate/cyclohexane 4:1) *Rf* 0.28

Analysis Found: C, 49.6; H, 6.4; N, 13.4

$C_{25}H_{38}N_6O_{11}.0.35C_4H_8O_2$ requires C, 49.6; H, 6.45; N, 13.9

(4S,5R,6R)-5-Acetylamino-4-amino-6-{2R,3-dihydroxy-1R-[(6-tert-butoxycarbonylaminohexyl)-carbamoyloxy]-propyl}-5,6-dihydro-4H-pyran-2-carboxylic acid trifluoroacetate

To a solution of Intermediate 9 (1.05 g) in dry tetrahydrofuran (40 ml) was added triphenylphosphine (610 mg) and the solution was stirred at room temperature for 18 hours. To this was added triethylamine (12 ml) and water (31 ml) and the solution was heated at 40° for a further 28 hours. The reaction mixture was evaporated to yield a yellow gum which was purified by flash reverse-phase chromatography (Merck 13900, water (containing trifluoroacetic acid 0.1%)/acetonitrile 8:2). The gum obtained by freeze-drying was triturated vigorously for one hour at room temperature to give the title compound as a buff powder.

NMR(d_6-DMSO) δ 7.92 (1H, d), 7.13 (1H, t), 6.75 (1H, t), 5.70 (1H, s) 4.85 (1H, d), 4.34 (1H, d), 4.02 (1H, q), 3.85 (1H, t), 3.77 (1H, d), 3.25, 3.44 (2H, m), 2.90 (4H, m), 1.82 (3H, s), 1.18-1.42 (8H, m), 1.38 (9H, s).

m/z MH^+=533

(1H, m), 3.3 (1H, m), 3.4 (1H, m), 2.91 (2H, m), 2.78 (2H, m), 1.81 (3H, s), 1.2-1.6 (8H, m)
m/z MH^+=475
TLC silica (butanol/acetic acid/water 3:1:1) R*f* 0.17

Example 6
(4S,5R,6R)-5-Acetylamino-4-amino-6-[1R-(1,1-dicyclohexylcarbamoyloxy)-2R,3-dihydroxypropyl]-5,6-dihydro-4H-pyran-2-carboxylic acid trifluoroacetate

Intermediate (11) (4S,5R,6R)-5-Acetylamino-4-azido-6-[(S)-(1,1-dicyclohexylcarbamoyloxy)-(2-oxo-[1,3]dioxolan-4R-yl)-methyl]-5,6-dihydro-4H-pyran-2-carboxylic acid benzhydryl ester
A mixture of Intermediate 4 (1 g) in dry pyridine, and dicyclohexylcarbamoyl chloride (1.46 g) was heated under nitrogen at 100 °C for six hours. The mixture was concentrated under vacuum and the residue treated with 30 % citric acid. The aqueous mixture was extracted with ethyl acetate (50ml x 2). The combined organic extracts were washed with 10 % sodium hydrogen carbonate solution (20ml), saturated aqueous NaCl (20ml), dried (Na_2SO_4) and the solvent removed under vacuum to yield an orange foam which was purified by flash chromatography on a silica column (Merck 9385, chloroform : methanol 20 : 1) to give the title compound (0.69g) as a colourless foam.
TLC silica (diethyl ether/pet.ether (40:60) 3:1) R*f* 0.14
Analysis Found: C, 65.6; H, 6.6; N, 9.4.
$C_{39}H_{49}N_5O_8$ requires C, 65.4; H, 6.9; N, 9.8

Intermediate (12) (4S,5R,6R)-5-Acetylamino-4-amino-6-[(S)-(1,1-dicyclohexylcarbamoyloxy)-(2-oxo-[1,3]dioxolan-4R-yl)-methyl]-5,6-dihydro-4H-pyran-2-carboxylic acid benzhydryl ester
The title compound was prepared from Intermediate 11 analogously to the preparation of Intermediate 6 from Intermediate 5.
NMR ($CDCl_3$) δ 7.3 (10H, m), 6.94 (1H, s), 6.1 (2H, m), 5.25 (1H, dd), 4.95 (1H, q), 4.6 (1H, dd), 4.4-4.1 (3H, m), 3.9 (1H, m), 3.6 (1H, m), 3.2 (2H, m), 2.05 (3H, s), 1.3 (3H, d), 1.8-1.0 (20H, m)
Analysis F und: C, 64.2; H, 6.9; N, 5.65
$C_{39}H_{51}N_3O_8.0.4CHCl_3$ requires C, 64.2; H, 7.0; N, 5.7

Example 10

(4S,5R,6R)-5-Acetylamino-4-amino-6-[1R-n-dodecylcarbamoyloxy-2R,3-dihydroxypropyl]-5,6-dihydro-4H-pyran-2-carboxylic acid trifluoroacetate

Prepared analogously to Example 1.

MS calc. for $C_{24}H_{44}N_3O_8$ MH^+:502.312841

Found: 502.314514

Analysis Found: C, 50.5; H, 7.35; N, 6.8

$C_{24}H_{43}N_3O_8.CF_3CO_2H$ requires: C, 50.7; H, 7.2; N, 6.8

Example 11

(4S,5R,6R)-5-Acetylamino-4-amino-6-[1R-(1,1-diisopropylcarbamoyloxy)-2R,3-dihydroxypropyl]-5,6-dihydro-4H-pyran-2-carboxylic acid trifluoroacetate

Prepared analogously to Example 6.

Analysis Found: C, 41.0; H, 5.5; N, 6.6

$C_{18}H_{31}N_3O_8.1.6\ CF_3CO_2H.H_2O$ requires: C, 41.2; H, 5.6; N, 6.8

TLC R*f* = 0.41, n-butanol : acetic acid : water, 3 : 1 : 1

Example 12

(4S,5R,6R)-5-Acetylamino-6-[1R-(1,1-diisopropylcarbamoyloxy)-2R,3-dihydroxy-propyl]-4-guanidino-5,6-dihydro-4H-pyran-2-carboxylic acid trifluoroacetate

Prepared analogously to Example 3.

MS calc. for $C_{19}H_{34}N_5O_8$ MH^+:460.240739

Found: 460.241167

Analysis Found: C, 42.8; H, 6.4; N, 11.45

$C_{19}H_{33}N_5O_8.CF_3CO_2H.H_2O$ requires: C, 42.6; H, 6.1; N, 11.8

Example 13

(4S,5R,6R)-5-Acetylamino-4-amino-6-[1R-(1,1-dibenzylcarbamoyloxy)-2R,3-dihydroxypropyl]-5,6-dihydro-4H-pyran-2-carboxylic acid trifluoroacetate

Prepared analogously to Example 4.

MS calc. for $C_{25}H_{32}N_3O_8$ MH+:514.218940

Found: 514.218791

TLC R*f* = 0.51, n-butanol : acetic acid : water, 3 : 1 : 1

(4S,5R,6R)-5-Acetylamino-6-[1R-(1,1-n-heptylbenzylcarbamoyloxy)-2R,3-dihydroxypropyl]-4-guanidino-5,6-dihydro-4H-pyran-2-carboxylic acid trifluoroacetate

Prepared analogously to Example 5.

Analysis Found: C, 48.3; H, 5.8; N, 9.6

$C_{27}H_{41}N_5O_8.1.5\ CF_3CO_2H.0.5H_2O$ requires: C, 48.45; H, 5.9; N, 9.4

TLC Rf = 0.58, n-butanol : acetic acid : water, 3 : 1 : 1

Example 19

(4S,5R,6R)-5-Acetylamino-4-amino-6-[1R-[(6-aminohexyl)carbamoyloxy]-2R,3-dihydroxypropyl]-5,6-dihydro-4H-pyran-2-carboxylic acid trifluoroacetate

Prepared analogously to Example 5.

MS calc. for $C_{18}H_{33}N_4O_8$ MH^+:433.229839

Found: 433.231597

TLC *Rf* = 0.12, n-butanol : acetic acid : water, 3 : 1 : 1

Example 20

Inhibition of Influenza Virus

The ability of compounds of the invention to inhibit the mutiplication of influenza virus was determined using the method described in WO91/16320. The compounds of the Examples showed activity against influenza A and influenza B virus in this plaque reduction assay. For example, compounds of Examples 1 to 5 had I_{50} values for influenza A and influenza B of less than 7μg/ml.